

# “Quantitative Pharmacology: An introduction to integrative pharmacokinetic-pharmacodynamic analysis”

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Dedicated textbooks in the area of integrative pharmacology are very scarce, notwithstanding the true need for educational narratives on the subject. It is therefore very gratifying that Johan Gabrielsson and Stephan Hjorth, both of whom carry a substantial track record (30yrs+) of industrial experience and academic research in pharmacokinetics and pharmacology, have taken the task on to fill this longstanding void.

The book focuses on why integration of pharmacokinetics (PK; what the body does to the drug) and pharmacodynamics (PD; what the drug does to the body) is so important in drug discovery and development. Gabrielsson/Hjorth embrace the subject matter both thoroughly and enthusiastically, with several illustrative real-world examples. Topics covered demonstrate well how an integrated approach may avoid the problems and pitfalls related to design of studies, analysis and interpretation of data. Practice examples for the reader are also, commendably, included. Divided into seven Chapters, the book instructively states the holistic approach intended by the authors. Given their affiliations in the Pharma environment it is logical that much emphasis is put on biomarkers, translational aspects and scaling from animal species to man. In my view, Gabrielsson/Hjorth have successfully achieved their stated purpose with the book.

The first Chapter sets the stage through a general introduction into the field of quantitative pharmacology and some of the terminology commonly encountered. A useful framework is described, on how to link drug- vs. system-specific properties using biomarkers as navigational tools, through a translational chain of events from geno/phenotype to clinical response in disease, and from animals to man. The book then goes on to examine the impact of PK upon our understanding of a pharmacological response. Chapter 2 sheds light on factors, confounders and challenges involved in connecting PK and PD for any given drug *in vivo* and points to complexities translating *in vitro* findings to *in vivo*. Chapter 3 focuses on various aspects of plasma protein binding and when it matters. A thought-provoking and illuminating example is the notably changed predictions of drug safety margins based on comparisons of *total* instead of *free unbound* plasma concentrations across animal models (*e.g.*, Fig 3.10). Throughout Chapters 2-3 the authors emphasize unbound (free) plasma concentrations for comparisons of results across species, compound and studies. This theme is echoed also in later Chapters (*cf.*, *e.g.*, Fig. 5.28), further stressing the importance of relating PD responses to drug levels actually encountered by the target biophase. Non-linearities commonly observed in drug discovery, and which sometimes confound the interpretation of pharmacological data, are discussed in Chapter 4, whereas Chapter 5 concisely presents rapid concentration-response equilibria. In the latter context, Fig. 5.26 illustrates a far from unknown, but often neglected, relation between receptor occupancy and response magnitude for some targets and drugs. Do comparisons of  $IC_{50}/EC_{50}$  values between different agents and across exposures always represent the most relevant measure in a given drug benefit/risk efficacy comparison?

Chapter 6 addresses the temporal disconnect sometimes found between plasma concentrations vs. target binding and physiological or disease biomarkers. In this context, the concept and usefulness of hysteresis

analysis is described by the authors in a very didactic fashion. They effectively explain the merits of this approach to re-connect two or more otherwise seemingly separate biomarkers; several Case Studies are also included – intended as potential practice examples for the interested reader. In the final Chapter the reader's attention is then focused upon the prospects of inter-species scaling of PK/PD properties from animals to humans – a task of utmost importance in the drug development perspective.

Taken together, the book emphasizes the importance of utilising *in vivo* data and thereby distances itself quite a bit from the commonly reductionistic use of *in vitro* data as a substitute for whole animal systems. I find this a very sympathetic approach that does a good job in uncovering the power of integrating PK and PD findings to optimise drug discovery and development. Mathematical equations and derivations are perhaps unavoidable in a book carrying integral PK content. However, the authors have strived to limit these and to maintain a high transparency in the understanding of complex and abstract relations using a nicely graphics-supported style throughout the presentation. Background acquaintance with PK and PD concepts is useful but not a prerequisite for the presumptive reader. To summarise, this book by Gabrielsson/Hjorth should provide very attractive and comprehensive reading for a broad audience – inside as well as outside Pharma – with interest in integrating PK and PD observations for greater understanding of how to connect drug fate and treatment consequences *in vivo*.